

Preimplantation Genetic Diagnosis and Savior Siblings

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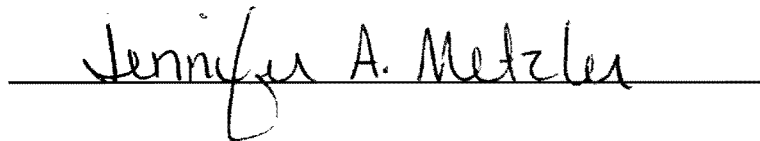
Preimplantation Genetic Diagnosis and Savior Siblings

An Honors Thesis – HONRS 499

By

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A handwritten signature in black ink, reading "Jennifer A. Metzler", is written over a horizontal line. The signature is cursive and fluid, with the first name "Jennifer" and last name "Metzler" clearly legible.

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Abstract

This project explores the controversial scientific topics of Preimplantation Genetic Diagnosis (PGD) and the creation of Savior Siblings. The history, basic procedures, risks, benefits, and ethical implications of both PGD and Savior Siblings are discussed in order to provide the knowledge base necessary to form personal conclusions on the use of these scientific advancements. Case studies from the United States, Australia and the United Kingdom, as well as regulations concerning the use of PGD, are discussed to illustrate the practical application of these controversial topics. Upon completion, readers will have sufficient knowledge of the ethical implications of both PGD and Savior Siblings to form their own opinions on what should and should not be allowed.

Preimplantation Genetic Diagnosis

History of Preimplantation Genetic Diagnosis

The development of Preimplantation Genetic Diagnosis, (PGD), began in order to offer treatment options to couples at risk of transmitting a genetic disorder to their offspring. Prior to PGD couples were forced to wait until 12 or 16 weeks into the pregnancy before undergoing prenatal testing. In the unfortunate event of a positive result for one of a number of genetic disorders, the parents would have to choose to continue the pregnancy or opt for an abortion (Gardner, Lane & Watson, 2004). Promising technology emerged in 1968 when scientists Edwards and Gardner completed the first known embryo biopsy on rabbit embryos. Ten years later, in 1978, the first “test-tube” baby was born using *in vitro* fertilization (IVF) (Dooley, McCarthy, Garanis-Papadatos, & Dalla-Vorgia, 2003). Technology continually increased the genetic capabilities during the mid 1980’s. The first successful birth of a healthy child resulting from PGD occurred in London in 1989. The mid 1990’s pioneered the use of fluorescence in situ hybridization (FISH) analysis for PGD of Aneuploidies, Chromosomal Translocations and common late onset disorders that are genetically predisposed. The actual FISH method will be discussed in the section on PGD procedure. The year 2000 brought about Preimplantation HLA Typing – the precursor to tissue typing. HLA stands for Human Leukocyte Antigen which are antigens found on the surface of most body cells. HLA antigens on the surface of white blood cells can be detected from a blood specimen. These antigens play a key role in the body’s recognition of foreign tissue; therefore, HLA matching is crucial in order for transplants to be successful. In 2002 a monumental milestone was hit when the 1000th PGD babies were born (Preimplantation Genetic Diagnosis International Society, 2004). Currently, PGD is the only

available alternative to procedures such as amniocentesis or chorionic villus sampling.

Unfavorable results of such postconception procedures often result in termination of pregnancy or continued pregnancies resulting in children born with birth defects (Marik, 2005).

PGD is therefore seen by many as a way to prevent the dilemma of having to choose between aborting an affected fetus or having a child born with a genetic disorder. Furthermore, PGD with tissue typing, a result of the discovery in 2000 of HLA typing, allows specialists today to select embryos that match an existing individual thus creating a "Savior Sibling" (Human Genetics Commission, 2005).

Current statistics vary; however, it is estimated that approximately 50,000 babies are born annually in the United States as a result of IVF (Singer, 2007). Furthermore, the Preimplantation Genetic Diagnosis International Society (PGDIS) states that approximately 30,000 PGD cycles have been performed around the world testing for over 170 different medical conditions (PGDIS, 2008). Santiago Munne, director of Reprogenetics a leading PGD company, states that his lab alone has tested embryos for more than 150 diseases including recent testing for BRCA1 which is linked to increased risk of breast cancer (Singer, 2007).

What is PGD?

PGD is a recently developed technique used to determine if a particular embryo, created outside the body using IVF, is affected by a genetic disorder. It is called *preimplantation* genetic diagnosis because it takes place before the embryo has attached itself to the uterine wall which usually occurs approximately six days after fertilization. IVF itself is a method of assisted reproduction in which the sperm and egg are combined in a laboratory dish to achieve fertilization. Successful fertilization results in an embryo which is then implanted into the

woman's uterus. Normally anywhere from 2 to 4 embryos are implanted at a time to increase the chances of successful pregnancy. IVF provides the foundation techniques needed in order to make PGD possible. The ability to form embryos *in vitro* is necessary in order to perform PGD procedures. The actual process of PGD involves IVF followed by the biopsy of polar bodies from oocytes, blastomeres from cleavage-stage embryos or trophectoderm cells from blastocysts. Then, cell diagnosis is performed by harvesting 1-2 cells from the embryo when it is at the 6-8 cell stage – usually about 3 days after fertilization (Gardner, Lane & Watson, 2004). Despite knowing that analysis of 2 cells is more accurate, common practice is to remove only 1 cell from the embryo to reduce the chance of damage to the embryo or developmental complications. The chances of embryo damage and developmental complications are increased with the removal of more cells because this lessens the number of cells left within in the embryo that are capable of making up for or correcting problems that may occur in the other embryonic cells. The human body has a powerful ability to self correct many problems; therefore, reducing the number of cells within the embryo limits the ability of the embryo to self correct should any problems arise (Silber, 2008). At this point all of the cells in the embryo are still undifferentiated and therefore capable of becoming all types of body cells. It is because of this undifferentiation that harvesting the cells does not damage the embryo's ability to mature. Common, reliable lab procedures including Polymerase Chain Reaction (PCR) and FISH are used to amplify and test the DNA (Marik, 2005). These procedures will be further discussed in the in depth section on PGD procedures. PGD can currently be used to detect single gene disorders, late onset disorders that have genetic predisposition, chromosomal disorders and HLA tissue typing to match for stem cell transplantation (PGIS, 2008). Commonly known disorders for

which PGD can be used include the following: Down syndrome, cystic fibrosis, muscular dystrophy, sickle cell anemia, Tay-Sachs and various forms of mental retardation.

Preimplantation genetic testing technology encompasses a number of different techniques that are used to achieve slightly different objectives. Along with testing for specific diseases, PGD can be used to determine the sex of an embryo. Sex determination enables Preimplantation sex selection which can ensure exclusion of sex-linked genetic disorders (Marik, 2005).

Conditions PGD Diagnoses

Current PGD technology can be used to test for three categories of disease including sex-linked disorders, single gene defects and chromosomal disorders. Sex-linked disorders are those disorders which are generally passed to a child through a mother who is a carrier. An individual who is a carrier has one dominant and one recessive allele (heterozygous) for a given gene. The dominant allele masks the recessive allele and therefore the disease is not present in a carrier. However, the recessive allele can still be passed on to the offspring thus creating the chance the offspring will be affected. The abnormal X chromosome is passed from the carrier mother to her son where it manifests the disease due to the presence of a Y chromosome from the father instead of a normal X. The sex-linked nature results in affected fathers having unaffected sons; however, their daughters have a 50% chance of being a carrier. Sex-linked disorders can be classified as either dominant or recessive. Sex-linked dominant disorders include Rett syndrome, incontinentia pigmenti, pseudohyperparathyroidism and vitamin D-resistant rickets. Common sex-linked recessive disorders include hemophilia, fragile X-syndrome, most muscular dystrophies and many other diseases. It is currently impossible to test for the exact genetic mutations for many sex-linked disorders due to technical limitations

as well as the mutation being unknown (HGC, 2005). Even though PGD cannot directly test for the disorder, it can be used to determine the sex of the embryo in order to selectively implant the sex least likely to be affected by a genetic disorder (Marik, 2005).

Single gene defects result in diseases such as Tay-Sachs disease, sickle cell anemia, cystic fibrosis, spinal muscular atrophy, myotonic dystrophy and Huntington's disease (HGC, 2005). Currently there are 25 single cell defects that are tested for using a process of PCR amplification of the DNA from one cell. Problems with testing for these defects revolve around each defect showing a large number of possible mutations responsible for the defect. Difficulties identifying all possible mutations can lead to false diagnosis (Marik, 2005).

The final category of disease PGD can be used to detect includes those characterized by chromosomal translocations, inversions and deletions. These types of chromosomal rearrangements can cause spontaneous miscarriage due to the disruption in the balance of chromosomes within an embryo (Marik, 2005).

PGD Procedure

The PGD process can be divided into the following five procedures IVF, embryo biopsy, single cell diagnosis, polymerase chain reaction (PCR) and fluorescent in situ hybridization (FISH). The initial IVF, as briefly described earlier, achieves fertilization outside the body by combining the sperm and egg in a Petri dish. The formed embryos can then be tested for genetic disorders prior to implantation. IVF, which is only used by about five percent of infertile couples, gives these couples the opportunity to have a child that is biologically theirs. The most common uses of IVF are to overcome infertility due to blocked, severely damaged or nonexistent fallopian tubes, complications of endometriosis and problems with a man's sperm.

(Gardner, et al., 2004) Of all of the embryos created through IVF approximately 25-30% have a chromosomal abnormality. These same types of abnormalities are found in approximately 62% of post IVF spontaneous abortions and in approximately 60% of spontaneous abortions following natural conception (Dickens, 2005).

The process of embryo biopsy can theoretically be done at three different stages in order to perform PGD. The first stage involves the removal of the first and second polar bodies. Polar bodies are extracted from egg cells and therefore contain only maternal chromosomes (Mahowald, 2000). This technique initially only required the removal of the first polar body which can be done before fertilization. This was therefore considered preconception diagnosis which helped many advocates defend the morality of PGD. However, it has since been determined that both polar bodies must be removed in order to assure accurate results. Removal of both polar bodies requires fertilization and removal of the second polar body from the zygote. Opponents of PGD argue this point by saying that once fertilization has occurred the embryo is in fact a living being. The second stage of embryo biopsy involves removing 10-20 trophectoderm cells from the blastocyst, the structure formed after the zygote stage and just before the embryo stage. The trophectoderm cells are from the trophoblast, the outer portion of the blastocyst which becomes the placenta. This procedure has the ability to yield a large number of cells; however, there are many drawbacks associated with biopsy at this stage. The most commonly used biopsy method involves waiting until the third day of development when the embryo is at the cleavage stage. At this point the embryo is usually anywhere from six to ten cells. Embryo biopsy at the cleavage stage requires extracting one or two cells; however,

usually only one cell is removed to lessen the risk of damage to future development (Gardner, et al., 2004).

Single cell diagnosis in PGD can be done using either PCR or FISH depending on the type of disorder being tested for. PCR is generally used for single gene defects, autosomal dominant and recessive disorders, specific determination of X-linked disorders and triplet repeat diseases. FISH examines chromosomes and therefore is used to sex embryos for X-linked diseases and to locate chromosome abnormalities such as translocations, insertions and deletions (Gardner, et al., 2004). Both procedures are extremely useful as they help to detect different types of genetic disorders.

PCR is the process of amplifying a certain, specific fragment of DNA thousands of times. The amplification is generally achieved using specific primers that are designed to target and amplify the area of DNA that has the mutation. Amplified DNA can be analyzed using heteroduplex analysis, single-stranded conformational polymorphism, restriction enzyme digestion and fluorescent PCR. PCR can be used to detect single-gene defects because most of these defects have specific locations where the mutation usually occurs. The PCR primers are therefore chosen to match the particular region of defect based on the specific mutation being tested. A major complication of PCR involves contamination and allele dropout (ADO) otherwise known as preferential amplification. Contamination can occur during the actual extraction procedure when cells or sperm cling to the biopsied cell. Contamination can also be caused by DNA found in the lab atmosphere or from lab workers. Although contamination is possible in all PCR reactions, the use of only one cell for diagnosis means that contamination often leads to

misdiagnosis. To avoid such misdiagnosis, polymorphic markers are often used to ensure the DNA being analyzed is from the parents and not a result of contamination. ADO occurs when one of the alleles in the pair does not amplify during PCR. ADO in a carrier individual would result in either only the dominant allele or only the recessive allele being amplified. ADO must be kept at a minimum especially in PCR being done for PGD due to the fact that a missing allele could mean the difference between a parent being unaffected or being a carrier. An actual carrier parent could be identified as normal if only a normal allele is amplified. Therefore, the very use of PGD to prevent the passage of genetic disorders is threatened by the problem of ADO (Gardner, et al., 2004).

FISH is the chosen procedure to analyze actual chromosomes. It is often used to supplement other chromosome analysis techniques such as typical karyotyping. Interphase FISH is the method most often used due to the difficulty in obtaining metaphase chromosomes. The two types of probes that can be used for Interphase FISH include repeat sequence probes and locus specific probes. Repeat sequence probes generally bind to the centromere or alpha satellite regions of a chromosome while the locus specific probes bind to a specific sequence of a chromosome. The probes are labeled with fluorochromes and are mixed with the chromosomes. Examination under a fluorescent microscope reveals fluorescent dots where the probes have bound with complementary DNA sequences. Until recently FISH was primarily used to sex embryos in order to avoid X-linked disorders in at risk couples. Recent technology has allowed three-color FISH to be used for embryo sexing and to identify extra chromosomes. The addition of the extra probe would ideally be a great way to detect and reduce the occurrence of Trisomy 21 or Down's syndrome; however, repeat probes for acrocentric chromosomes are

extremely inefficient. The presence of the centromere very close to one end in acrocentric chromosomes causes these chromosomes to cross-hybridize resulting in the inefficiency. Just as misdiagnosis problems occur with PCR, FISH also runs the chance of producing false results due to the occurrence of mosaicism within an embryo. Mosaicism occurs when there are some normal and some affected cells within the same embryo. Since PGD generally removes only one cell from the embryo there is a chance that this one cell does not match the rest of the cells and therefore could lead to a misdiagnosis. This is a problem specifically associated with FISH because normal and abnormal chromosomes are often seen within the same embryo (Gardner, et al., 2004).

Benefits of PGD

PGD has a number of advantages which make the procedure extremely desirable to at risk couples. Perhaps the biggest benefit of PGD technology is that it allows at risk parents to have children without facing the heartbreaking decision that comes with the postconception discovery of a child with a genetic disorder (PGDIS, 2004). While other prenatal diagnosis methods can detect disorders before birth, the parents are still forced to choose between aborting a pregnancy that is often fairly advanced or delivering a child with a serious, often fatal genetic disorder. Therefore, PGD is seen by many as a direct alternative to termination of pregnancy. The uses of PGD have expanded from simply genetic diagnosis to include, detection of chromosomal abnormalities, chromosomal tissue typing for implantation compatibility and sex-selection to eliminate carrier embryos for sex-linked disorders (Dickens, 2005).

Limitations of PGD

PGD, like any other intricate medical procedure, has a number of negative aspects that weigh on the minds of doctors and potential candidates alike. The major problems associated with PGD stem from the complex nature of the procedure, the need for a large number of embryos for successful IVF and the current stage of PGD technology (Marik, 2005). The complex nature of the actual IVF and PGD procedures results in only approximately 20% of PGD treatment cycles actually resulting in a live birth (HGC, 2005). Main areas of concern include the risk associated with embryo biopsy and cell removal, the lack of unaffected embryos resulting from IVF and possibly misdiagnosis. Procedural complications during the biopsy result from the extreme difficulty of removing a single cell from the embryo without breaking the cell or causing damage to the embryo. Furthermore, successful completion of the highly technical procedure does not guarantee pregnancy or by any means a full-term pregnancy. Women undergoing PGD typically endure five cycles of IVF before successfully becoming pregnant (Marik, 2005).

The success of any PGD procedure is dependent upon the presence of a large pool of candidate embryos within which hopefully some are unaffected. The need for a large number of possible embryos requires hyperstimulation of the ovaries which in many cases has undesirable side effects. Sometimes despite enduring the mental and physical stress there are few or no unaffected embryos available making the cycle a failure. On the opposite end of the spectrum, IVF often involves implantation of multiple embryos to increase the likelihood that pregnancy occurs. While it is generally the case that only one or no embryos result in

pregnancy, sometimes multiple pregnancies do occur. This is a complication many countries avoid by enforcing single implantation at the cost of lowered chances of success.

Another concern for complications involves the current technological capabilities of PGD and the research and advancement to be expected in the future. The current method of PGD involves analysis of a single biopsied cell. Analysis of a single cell is very difficult and can easily lead to misdiagnosis. To remedy any possible misdiagnosis common prenatal testing is often done to confirm that the embryo is in fact unaffected. Furthermore, single cell biopsy currently only allows each cell to be tested for a single specific defect. Cells cannot be blindly tested for all genetic disorders because PCR and FISH require certain sequences to be pinpointed for amplification and hybridization, respectively. Therefore, each cell extracted from an embryo cannot be screened for a wide range of genetic defects. This makes PGD useful when a specific threat for genetic disorder exists in a family, but practically useless to screen against a range of genetic defects just to ensure a healthy child. The technological state of PGD has come a long way since 1989; however, there are still plenty of advances to be made. At present, there are many genetic disorders which PGD cannot detect due to the unknown cause of the disorder. Developing the expertise to diagnose new diseases is time consuming and expensive; therefore, resources will be the key factor to expanding PGD capabilities (Marik, 2005).

Candidates for PGD

PGD is useful for a number of candidates largely due to the capabilities of PCR and FISH to examine embryos for single gene defects (PCR) and chromosomal abnormalities (FISH). Candidates for PGD fall into three general categories including those who have increased risk of passing on a genetic or chromosomal disorder, those who have had problems with fertility and in many cases IVF and those who already have children with a disorder PGD can test for.

Increased risk of passing on a genetic or chromosomal disorder can come from having a family history of genetic disease, being a known carrier for a genetic disease and being a known carrier of a chromosomal abnormality such as translocation. Therefore, couples in all of those situations make good PGD candidates. A family history of genetic disorders can result in parents who are carriers for a particular genetic disease without those parents showing signs of the disease. PGD can help stop the unexpected birth of an affected child to two seemingly healthy parents. Carriers of single gene disorders can use PGD to have a healthy child, and in many cases have a healthy child who is a tissue match to an ill child.

PGD can also be a helpful tool for couples who have had infertility problems and may or may not have already tried IVF. Couples who could benefit from PGD for this reason are those in which the woman is 35 years or older, couples that experience certain male infertility problems, couples experiencing recurrent IVF failures and couples experiencing repeated spontaneous abortions or trisomic conceptions. Women 35 years and older are prime candidates for aneuploidy disorders, such as trisomy 21 commonly known as Down Syndrome and could therefore benefit immensely from PGD (Marik, 2005). Regardless of age, any woman who has experienced recurring failures with IVF and pregnancy could benefit from PGD due to

its higher implantation rates and reduction in spontaneous abortion and chromosomal abnormality rates (Reprogenetics, 2001).

The last category includes parents that have previous children who are affected by a disorder that PGD can test for. Use of PGD by these couples could be simply to prevent having more children with the disease or to try and have a child that is a tissue match and can therefore be a donor to the previous child (Marik, 2005). Couples that could benefit from PGD for this reason include those who have a child with mental or physical disorders, those who have a child with a diagnosed genetic disorder and those who wish to undergo HLA typing to conceive a child matched to an older sibling for the purpose of stem cell therapy to cure an existing disorder (PGIS, 2008).

Statistics from United States Providers

The fact that very little data exists concerning the extent to which PGD is actually used prompted the Genetics and Public Policy Center at Johns Hopkins University to publish a report containing some of the first and only PGD figures in the nation. Susannah Baruch, lead author of the report and director of reproductive genetics explained the survey saying, "We wanted to get a sense of how much PGD was being done, and why. Without solid data, it is difficult to analyze outcomes for PGD babies or to help prospective parents make decisions about whether to pursue PGD." The survey which was conducted at all U.S. fertility clinics that offer IVF included questions concerning specific tests offered, ethical considerations and thoughts on PGD regulation. Of those surveyed only about half of the clinics responded. The results showed that approximately two-thirds of all PGD testing is done to diagnose chromosomal abnormalities and disorders linked to chromosome deletion or duplication while only twelve

percent of testing is done to detect specific genetic diseases. Forty-three percent of PGD providing clinics said they had received procedural requests that “raise ethical questions” – most often sex selection for nonmedical reasons (Singer, 2007). On a more general basis, more than seventy percent of respondents approved the use of PGD to avoid serious disease; however, less than thirty percent approved the use of PGD to choose sex or other desired traits (Landhuis, 2004).

Savior Siblings

PGD with Tissue Typing

The concept of PGD is taken a step further with the ability to select an embryo that matches, and therefore could be a donor, for a child with one of a number of serious disorders such as Fanconi Anaemia, β -Thalassaemia and Diamond-Blackfan anaemia. The process is the same as PGD with an extra test being done to determine the compatibility between the existing individual and the embryo. The ideal outcome of PGD with tissue typing is a child whose umbilical cord blood or bone marrow can be given to the ill sibling (HGC, 2005). A report based on consultation by the HGC advised the UK government to take extreme caution when approaching the topic of PGD and tissue typing. Helena Kennedy, chairwoman of the HGC stated, “With the accelerating pace of genetic research, the possibilities for couples experiencing fertility problems or families with a history of genetic illnesses are now considerable and increasing.” The HGC stressed the need for thorough follow-up of children born after PGD as there is relatively little evidence about the long term safety of the procedure. In fact, the commission called for legislative changes concerning confidentiality issues that make follow-up of PGD children difficult (Mayor, 2006).

Benefits of Tissue Typing

The benefits of PGD, especially with tissue typing, are immeasurable to a family that has a child affected by a genetic disorder. Not only can PGD allow the assurance that subsequent children will not be affected, but tissue typing can result in a healthy child that can possibly be a savior for its sick sibling (HGC, 2005). PGD with tissue typing has the ability to save a number of children who would die without their savior sibling. J. Glover stated in the BBC News, “You have got to have a very powerful reason to resist the means by which a child’s life can be saved” (Sheldon, S. & Wilkinson, S., 2004).

Limitations of Tissue Typing

Unfortunately, PGD with tissue typing is only currently available for a limited number of serious genetic conditions usually those treatable through stem cell transplant. Along with the limited number of disorders this technique can treat, PGD with tissue typing is also limited by success rate, selection process, side-effects and safety. With PGD itself being extremely difficult, PGD with tissue typing is a technically challenging and very complex procedure. The selection of a “Savior Sibling” embryo is difficult and requires a large number of embryos to choose from. Not only must the selected embryo be free from the genetic disorder, it now must also be a specific HLA match. Doubling of the criteria brings the chance of an embryo that is an unaffected match to 3 out of every 16 embryos for an autosomal recessive disorder. Side-effects from the large number of embryos needed arise from hyper-stimulation of the ovaries and laparoscopic collection of the eggs. Lastly, the relatively new procedure lacks a well-established track record and any real knowledge of the long term effects on the mother, “savior sibling” or the child with the illness (HGC, 2005). Other common arguments against PGD with

tissue typing include the savior sibling being treated as a commodity, a concern for the welfare of the savior sibling and the slippery slope from savior siblings to “designer babies” (Sheldon, S. & Wilkinson, S., 2004). These topics will be discussed in the following section as well as in the section concerning ethical implications.

Case Studies

United States – The Nash family had a 6 year old daughter, Molly, who suffered from “rapidly progressive bone marrow failure and myelodysplastic syndrome secondary to Fanconi anaemia, an inherited rare, but fatal disorder associated with leukemia and predisposition to cancer.” The controversial nature of PGD led the Nash family to seek ethical approval to have IVF performed in Colorado, PGD in Chicago and embryo transplant in Minnesota. The Nash’s had to undergo four attempts before giving birth to Adam Nash on August 29, 2000 (Lee, 2002). Adam did not inherit the Fanconi anaemia, and he was found to be a compatible donor of placenta and umbilical cord blood stem cells. Adam was used as a transplant donor for Molly, and within 4 weeks Molly had shown bone marrow recovery. Three years after the transplant tests confirmed that Molly’s hematopoietic and immune systems had recovered and were normal (Dickens, 2005).

Australia – A Victoria couple was given permission to use PGD and tissue typing technology to create a savior sibling in hopes of saving their three year old daughter Christina from Fanconi anaemia. The permission was given by the Infertility Treatment Authority (ITA), the authoritative body overseeing IVF in Australia. Although this case was approved, Australia’s policy does have some specific conditions. PGD with tissue typing can only be used to save a

terminally ill sibling not a husband or wife. Furthermore, the savior sibling can only donate cord blood or bone marrow; transplant of organs such as kidneys is not allowed. The decision of the ITA to approve certain PGD and tissue typing procedures sparked a wide range of reactions as is seen in many countries (Spriggs, M. & Savulescu, J., 2002).

United Kingdom – The Hashmi, Whitaker and Fletcher families are further cases in which PGD has been sought as a means to save an existing child. The Hashmi family petitioned the Human Fertilization and Embryology Authority (HFEA) for approval for IVF and PGD with tissue typing in order to conceive a child that would be a savior to their six year old son, Zain. The PGD child would hopefully be free from β -Thalassaemia Major and would therefore provide the otherwise unavailable stem cells needed to save Zain's life (Dyer, 2005). Although challenged by conservative activist groups opposed to the misuse of embryos and abortion, the HFEA interpreted the UK 1990 Act (further described under regulations) as giving the authority to approve the procedures. Furthermore, the HFEA approved PGD to test for specified conditions late in 2001. Unfortunately, after undergoing IVF and PGD Mrs. Hashmi miscarried in December of 2003. The family continued trying; however, after six rounds of IVF they decided not to undergo any further attempts (Dickens, 2005). Lord Hoffmann, a member of the UK's highest court supported PGD and tissue typing saying it was, "a way to save the Hashmi family from having to play dice with conception" (Dyer, 2005).

The Whitaker family requested HFEA approval of IVF and embryo screening just as the Hashmi case gained national attention. The Whitakers were looking to conceive a child that would be a bone marrow donor for their three year old son, Charlie, who suffered from

Diamond-Blackfan anaemia. Although it was believed the condition may be associated with a genetic mutation, the exact cause was unknown. The prognosis for Diamond-Blackfan anaemia involved blood transfusions every 3 weeks and a maximum life expectancy of only 30 years. A bone marrow transplant from a compatible donor was their son's only chance; unfortunately, the HFEA refused approval in July of 2002. The distinction the HFEA made highlights the controversy as to what PGD uses are acceptable. The HFEA determined that the Hashmis were at risk of having another child with the same inherited genetic disorder as their son; therefore, the PGD was justified to prevent passage of the genetic disorder. Since the cause of Diamond-Blackfan anemia was unknown, the HFEA concluded that the Whitakers were not at risk of transmitting the disorder Charlie suffered from. The HFEA refused the request because it felt the Whitakers request for IVF and PGD with tissue typing was solely to create a compatible tissue donor – not to prevent the risk of inheriting a genetic disorder. In essence the HFEA determined that the Hashmi's request was for the purpose of promoting medical health while the Whitaker's request was for purely social purposes. Critics of the HFEA decision argue that the UK policy "failed to keep up with the benefits that new technology can bring" (Dobson, 2003). Disagreement with the HFEA's decision was evident when the Whitakers received a great deal of sympathy on their October 2002 visit to the Chicago clinic that treated the Nash family. The Whitakers gave birth to their daughter Jamie who was confirmed to be a close tissue match to Charlie. Upon confirmation that Jamie did not have the disorder, the stem cell transplant was performed. Early signs of progress following the transplant were promising; however, it would take at least a year for five year old Charlie to begin producing his own healthy red blood cells and therefore be cured (Dickens, 2005).

Despite the Whitaker's failure to gain HFEA approval to have PGD and tissue typing performed in the UK, the Fletcher family decided to try their case in April 2004. The Fletchers requested IVF and PGD of embryos in order to treat their two year old son who suffered from Diamond-Blackfan anaemia just as in the Whitaker case. The Fletcher's physician stated that they were prepared to challenge the HFEA's refusal with judicial proceedings. The family had even remortgaged their home in order to have the money necessary to travel to Chicago for treatment if necessary. Recent evidence supporting the safety of PGD for children born from the process contributed to the HFEA's change in policy since the Whitaker case. Fortunately for the Fletchers, in September 2004 the HFEA approved a license for the IVF and PGD treatment to be done in the United Kingdom. This was the first case to be approved under the HFEA's new policy on the use of PGD (Dickens, 2005). The HFEA continues to give approval "in principle" to PGD and tissue typing; however, applications are considered on a "case by case" basis. Ruth Deech, HFEA chairman, stated that, "Licenses will be subject to strict conditions. Where PGD is already being undertaken we can see how the use of tissue typing to save the life of a sibling could be justified. We would see this happening only in very rare circumstances and under strict controls" (Spriggs, M. & Savulescu, J., 2002).

Impact on the Savior Sibling

The impact on the savior sibling and the recipient is largely due to the extent the savior sibling serves as a donor. Since negative consequences are more closely associated with the savior sibling than the recipient we will focus on the former. In many cases the stem cells needed for transplant are acquired from the placenta or umbilical cord blood; therefore, the newborn child does not suffer any bodily harm. In situations where the savior sibling is born

and is a direct donor of blood or bone marrow there is more of a concern for the welfare of the child. From a physical perspective, a savior sibling donating blood or stem cells makes a notable sacrifice for his or her sibling (Dickens, 2005). The extent of direct donation can vary as some disorders and situations require multiple transplants. Opponents of PGD with tissue typing argue that cases which require multiple donations by the savior sibling place an unnecessary and unfair burden on this child. Molly Nash could potentially be a great example of this as people with Fanconi's anemia often suffer from other organ problems and an increased susceptibility to cancers especially leukemia. As Molly ages she may need Adam's bone marrow to treat leukemia or a kidney to treat renal failure (Turner, 2002). Would these requests be asking too much?

Along with the physical burden, many opponents argue that the savior sibling could be psychologically scarred as well. The two main arguments are that the savior sibling will suffer as a result of finding out that he or she was wanted in order to save another sibling, and the child will have less of a close, loving relationship with the parents since this child was wanted to save the previous child. Patrick Cusworth, spokesman for the UK pro-life charity LIFE said, "To create another child as a transplant source could set a dangerous precedent for uses of this kind of technology. How will baby Jamie (Whitaker) feel, for example, when she discovers that she was brought into the world to supply 'spare parts' for her elder brother?" (Dobson, 2003). In response to both arguments JA Robertson points out, "the fact that the parents are willing to conceive another child to protect the first suggests that they are highly committed to the well-being of their children, and that they will value the second child for its own sake as well" (Sheldon S. & Wilkinson, S., 2004).

Ethical Implications

Embryos

The debate concerning the rights of an embryo compared to those attributed to a fetus, child or adult is the center of most of the controversy surrounding the use of PGD. To clarify, the term embryo is used to describe the organism as it grows during the second through eighth weeks of its life. Although the embryo is initially only a tiny cluster of cells, by the eighth week the embryo is clearly identifiable as a human and then moves into the fetus stage. The word fetus is used to describe the organism from the third month up until birth (Gardner, et al., 2004). Many opponents of PGD believe that from the very instant of conception the embryo is a human life and therefore deserves the respect more commonly and easily given to a fetus, child or adult. Opponents therefore believe the deliberate choosing of which embryos should live should be viewed the same as the choice as to which fetuses or born individuals should be allowed to live (HGC, 2005).

The goal of PGD is to avoid implantation of affected embryos; therefore, it is understandable from a scientific perspective that the affected embryos are not implanted. However, many people overlook the fact that generally only one to a few embryos out of all of those found to be healthy are implanted. The remaining embryos, despite being healthy, are often either frozen or die. While the disregard for what PGD opponents consider a human life is seen as immoral in itself, the fact that healthy embryos are also often lost in the process is an even greater outrage. Ironically, the same loss of healthy embryos occurs during regular IVF; however, people in general seem to be more comfortable with this situation than in PGD. Is this simply because PGD is a newer advancement that people are not yet comfortable with? Or, is

the argument of loss of healthy embryos just a front for people's true concerns about the extreme capabilities and uncertain future of PGD? Some PGD opponents have concluded that PGD is morally worse than termination of pregnancy based on the potential of more embryos being destroyed at once (HGC, 2005). In fact, data released by the Chicago clinic which treated the Nash and Whitaker families highlights the substantial volume of embryos lost. The data showed that during the treatment of nine couples with children suffering from leukemia or anemia, 199 embryos were tested, 45 embryos were tissue-matches and identified for implantation, 28 were actually used over 12 cycles of IVF and 5 pregnancies resulted (Dickens, 2005). The PGDIS does not advocate discarding unused embryos; instead, it states that spare embryos should be frozen via cryopreservation or retested to confirm the initial PGD results. Cryopreservation has historically been looked down upon due to low success rates; however, recent advances in technology have greatly improved the preservation rates using this method. Embryos not implanted or cryopreserved should be retested with examination of all blastomeres of each embryo. Retesting embryos for means of confirmation of results is especially important when the single-cell method of analysis is used to ensure that the error rate can be held under 10% (PGDIS, 2008).

The opposing viewpoint is that the Preimplantation embryo is less human than a fetus making elimination of a PGD embryo less severe than termination of a pregnancy. Those who believe the embryo stage is somehow less human than subsequent stages of development view the embryo as just "tissue" not a living being. Advocates of PGD believe that it is more ethical to discover a severe genetic disorder at the Preimplantation state where the pregnancy can be

avoided completely rather than to wait and perform typical prenatal diagnostic testing (PND) often resulting in pregnancy termination (HGC, 2005).

Cells lost to process

The single cell that was harvested could have developed into a fetus; therefore harvesting that cell for testing purposes is seen by opponents as murder. In addition, all fertilized cells that are found to be affected by the disorder are allowed to die in the Petri dish. Advocates argue that if affected cells develop into pregnancy and eventually a live birth, the child would be at a disadvantage due to the disorder (Marik, 2005).

Disability and Society

A series of European funded interviews were conducted with “disabled” young adults in order to determine the implications of the increased usage of prenatal counseling and scientific technologies like PGD on people currently living with the troubling diseases parents today are so desperately trying to avoid. The interviewees told stories of their lives, their families and their friends. Although many experienced considerable pain and difficulty as a result of their disease, most seemed to value their lives as well as be valued by their family and friends. Despite the hand they had been dealt, none of the interviewees expressed the desire to end their lives or that their lives would have been better off prevented through a procedure such as PGD. When asked about living with a disability the interviewees continually talked about the importance of being made to feel a part of mainstream society. Many felt that the pain of rejection from society was worse than pain and difficulty directly resulting from their disease. Furthermore, Deborah Kaplan is cited as saying that there is, “an emerging disability rights movement built on the belief that many problems experienced by person with disabilities,

problems which seriously interfere with the quality of their lives are caused, not solely by the impairment, but by the ignorance of other people, the fear of difference and by the barriers that exist in society, whether they are architectural, institutional, technological, legal or attitudinal” (Dooley, et al., 2004). The group of individuals provided evidence against the belief that prenatal testing, counseling and prevention of lives is an ethically acceptable practice. Such individuals directly challenge the justification that termination of all affected pregnancies, regardless of severity, is preferable to risking the terrible outcome of the most severe cases (Dickenson, 2002).

Many individuals living with the diseases prenatal counseling seeks to avoid fear that procedures such as PGD could be interpreted as “official medical endorsement” of the prejudices society already holds against them. The individuals explained the sense of accomplishment they had gained from adapting to and overcoming their disability. These individuals feel that prenatal screening seeks to shelter and keep individuals from the difficulties associated with disabilities as if humans should not have to experience any difficulty. Life itself is filled with difficulty; individuals born with a disability feel they just have one more difficulty to face than others (Dickenson, 2002).

The idea of “official medical endorsement” is taken a step further to official *government* endorsement through programs such as state- funded prenatal screening. Individuals with disabilities feel that such programs are open endorsements of the discrimination society holds against impaired people. Such programs reinforce ideas that people with disabilities are more of a burden to society than they are worth, and that society is better off preventing the birth of

disabled people than dealing with the burden of their care. Such discrimination results in an increase of social exclusion, school exclusion and family exclusion as well as an increase in adherence to certain school tests, milestones, and behavioral standards. Specifically, the “zero-tolerance” policy does not account for contingencies and disadvantages when applying standards. Although prenatal testing does not directly result in such policies, such testing does provide strong medical and governmental endorsements of the societal discrimination against people with disabilities (Dickenson, 2002).

PGD for Sex Selection

The ability of PGD to determine the sex of the embryo has prompted many couples to seek PGD for the purpose of sex selection completely apart from disease prevention. Although in most countries PGD is only used to diagnose serious chromosomal or genetic diseases or to identify aneuploidy in older IVF patients, PGD for sex selection has been undertaken in a very small number of countries. In 2004 one such country, Jordan, had seen 250 cycles of PGD specifically for sex selection. Of these 250 cases only 1 couple had selected for a girl (Gardner, et al., 2004). Various personal, cultural, social, ethnic and psychological reasons drive parents to desire the power to choose the sex of their child. Most people think that the preference for male children is limited to developing countries; however, data from sex-preselection cases in the United States show that 84% of couples choosing their child’s sex prefer to have sons (Mahowald, 2000). Families who wish to choose the sex of a child often hope to achieve a “balanced family” or are trying to avoid having all of their children be of the same gender. Using PGD for sex selection has sparked extreme controversy as it is seen as the beginning of the slippery slope leading to the creation of designer babies. Arguments against sex selection

include the discarding of embryos not of the chosen sex being an act of infanticide, sex discrimination, continued oppression of females and the ever expanding capabilities of control over non life threatening characteristics of offspring (Marik, 2005).

Responsibility to Future Generations

Now that scientific capabilities such as PGD allow for the selection of healthy embryos for implantation, the question of duty to future generations becomes an important ethical consideration. Not only does PGD enable at risk families to have healthy children, it also opens the door to the capability of eliminating genetically transmitted diseases from future generations. PGD, if performed diligently in at risk cases, could significantly reduce the number of births affected by genetic disease until the diseases are effectively eliminated. Now that science is capable of identifying and avoiding pregnancies leading to affected children, is it the responsibility of the current generation to do so? An even more interesting question is exactly what future generation is being helped by PGD? The question of obligation to future generations suggests that maybe PGD should be required in at risk cases; however, the controversial nature of the procedure will likely keep that from happening (Dickenson, 2002).

Therapeutic or Enhancement

The use of PGD is often broken down into genetic testing for “therapeutic” purposes and for “enhancement” purposes. Therapeutic uses include screening for genetic and chromosomal abnormalities in order to implant only the embryos that are not affected with a certain disorder. The use of PGD for enhancement purposes refers to “the use of such testing to select for improved traits that, without improvement, would lie within normal ranges.” That is to say that PGD for enhancement is when PGD is used to select for certain advantageous traits

that are not in any way life threatening. This is the premise for the creation of the “perfect child” (Dooley, et al., 2004). Enhancement of human beings, often generally referred to as eugenics, can be both positive and negative in nature. Positive eugenics is the use of technology to try and produce superior individuals or individuals with certain desired traits. On the other hand, negative eugenics looks to improve humanity by eliminating people with inferior traits. PGD is capable of accomplishing both of these motives; however, it is up to humanity to determine which uses are ethical and which should not be permitted. The most difficult question surrounding PGD focuses less on the current practices and more on what continued technological advances will mean for the future of PGD. Current uses for PGD include preventative selection against genetic disorders and tissue typing to select for stem cell donor matches for sick siblings; however, the latter selection for a particular trait is seen by many as the beginning of a slippery slope towards selection of traits to create the “perfect child” (Dickenson, 152).

Slippery Slope

Some people argue that PGD with tissue typing and the creation of savior siblings is the first step onto a slippery slope of scientific manipulation. Such uses of science are seen as destined to result in the building of “designer babies” much like people today build designer automobiles. There are generally three categories of thought including the following: people who oppose PGD and savior siblings altogether, people who support PGD and the creation of savior siblings but not the creation of “designer babies” and people who support the use of scientific advancements in all ways possible. Those people who oppose PGD and savior siblings believe that the entire concept of selection of embryos for specific characteristics is wrong.

Those people who support the creation of savior siblings but oppose the creation of “designer babies” believe that embryo selection is only appropriate for avoidance of genetic disorders and to save the life of a previous sibling. These people see a distinct difference between a savior sibling and a “designer baby.” Advocates of savior sibling technology and its continued advancement argue that savior siblings and designer babies are essentially the same thing since both are “selected” for. Therefore, these people believe that if one practice should be allowed then so should the other (Sheldon, et al., 2004).

The question of whether PGD will lead parents to seek scientific technology in order to create a “perfect” baby led to the 1999 release of a joint document from the HFEA and the Advisory Committee on Genetic Testing (ACGT) stating that, “Neither body thinks it would be acceptable to test for any social or psychological characteristics, normal physical variations, or any other conditions which are not associated with disability or a serious medical condition” (Dickenson, 2002). Currently each individual cell can only undergo one test; therefore, technology lends itself to testing for specific family history related disorders not just overall screening. Although the current technological capabilities prohibit simultaneous selection for desired traits, it is only a matter of time before technology will make designer babies a reality. (Marik, 2005).

When PGD is Acceptable

Future trends in PGD are understandably the area of most concern. The Human Fertilization and Embryology Authority (HFEA) echoes this concern when questioning what criteria should be used to determine when PGD is appropriate. Such criteria could include “expectancy of a very short life, a life of poor quality, or one of great suffering.” However, current technology is limited in its ability to determine how severe impairment may become. Furthermore, no one can determine how the family of the individual will react and support the person and how the stresses of social prejudice will affect the individual. Difficulty predicting length and quality of life makes the acceptance of PGD a grey area to say the least. Many parents and families cherish the life of a child regardless of the years lived, and they believe any time together is worth whatever struggles they encounter (Dickenson 208).

Who Decides Which Embryos will Lead “Better” Lives

In some cases the parents wish to undergo PGD in order to select for a commonly perceived “disability” with the belief that the public is wrong and the disability does not hinder the life of the individual. This attitude tends to be more common when dealing with achondroplasia and deafness than other genetic disorders. For example, some deaf parents wish to implant an embryo known to be affected by deafness rather than or in addition to unaffected embryos. The parent’s argument usually centers on the belief that being deaf is not a disability and in some cases is a better life than being hearing. Many deaf parents feel that having a hearing child would be more of a disadvantage to the child and family than having a deaf child because the child would be an outsider within the family. Very similar arguments accompany the choice to implant an embryo affected with achondroplasia rather than an

unaffected embryo. These cases question the definitions of disability and quality of life and tend to ignite heated controversy between those with disabilities and both the medical and social worlds. A general definition of disability as stated by John Harris in the text *The Ethics of New Reproductive Technologies* states that a disability is a, “physical or mental condition that we have a strong, rational, preference not to be in and it is, more importantly, a condition which is, in some sense a ‘harmed condition’.” He further suggests that disabilities should be looked at under the assumption that a completely successful, risk free cure was available. In this situation would it be ethical for a parent to withhold such treatment from a child in order to keep the child “disabled”? Determining what exactly disabled means, and whether or not parents should be able to select in favor of an affected embryo is a very difficult, complicated argument. As it appears, PGD can be used to select for or against a genetic disorder depending on the beliefs of the parents. This is yet another controversial implication of PGD (Dooley, et al., 2003).

The Preimplantation Genetic Diagnosis International Society (PGDIS)

Establishment of PGDIS

Annual meetings of the International Working Group on Preimplantation Genetics along with the International Symposia on Preimplantation Genetics laid the tracks for the development of a group dedicated to PGD and its future. The PGDIS was founded in the fall of 2002, and was inaugurated less than a year later at the 5th International Symposium on Preimplantation Genetics held in Turkey in 2003. Members of both the 4th and 5th Symposia are credited with creating the PGDIS with the purpose of “encouraging and coordinating

research, education and training in this multidisciplinary field, requiring close collaboration of reproductive medicine physicians, fertility specialists, embryologists and human geneticists (PGIS, 2008; Kuliev and Verlinsky, 2004). The society was formed with the goal of providing a close network of specialists so that the practices of PGD could be safely and accurately improved upon (PGDIS, 2004).

Guidelines for good Practice in PGD

Since a main goal of the PGDIS is to improve the safety and accuracy of PGD, the group published a set of voluntary guidelines available to all medical centers offering PGD. The original guidelines, published in 2004, have since been updated based on the current status of PGD technology. The purpose of the PGDIS guidelines is to provide an educational instrument to help clinics offer their patients the best PGD experience possible. The document begins with an overview of PGD including where today's technology stands. Other introductory sections include PGD indications, set-up of a PGD program and patient management. The middle sections outline specific procedures including IVF stimulation protocols, IVF and insemination, source of DNA for PGD and biopsy methods, PCR for single-gene disorders, PGD for chromosomal disorders and embryo transfer. Each of these sections gives a detailed description of what the PGDIS feels is the best protocol for each procedure. The final sections discuss the handling of spare embryos, follow-up of pregnancies, quality control and assurance and future perspectives. In addition to the text, the document includes a table listing all of the diseases for which PGD has successfully been performed as of November 22, 2007. Although each section outlines what the PGDIS believes is the best method to achieve overall PGD success, the society understands that these are in fact only voluntary guidelines. Furthermore, the PGDIS

acknowledges that differences in culture, beliefs and national regulations affect the administration of PGD around the world. Even though the guidelines for good practice in PGD are not enforceable laws or regulations, the PGDIS feels that such documents will help further the improvement of PGD safety and accuracy around the world (PGDIS, 2008).

Regulation

PGD acceptance and regulation varies throughout the world. Levels of PGD regulation range from complete bans on PGD to a lack of regulation at all (HGC, 2005). Some intermediate levels of regulation include national oversight committees to monitor PGD use. Many early laws were created before the use of PGD and therefore address medical assistance of reproduction in general, not specifically referring to PGD. One such law is the United Kingdom's Human Fertilisation and Embryology Act of 1990 which outlined prohibited activities in connection with embryos and gametes. This act also established the Human Fertilisation and Embryology Authority to administer and regulate reproduction assistance. Both France and Norway implemented laws in 1994 that basically allow for the therapeutic uses of PGD but do not allow PGD to be used for enhancement purposes or sex-selection. France's law states that in order for PGD to be performed a physician must determine that there is an irregularity in the parents that causes an increased probability that the embryo will be affected by a genetic or chromosomal abnormality. PGD may only be used to detect such disorders and to either prevent or cure the disorder. Norway's law allows for the use of PGD for detection of, "serious, untreatable, hereditary diseases," and it bans PGD use for sex-selection. Denmark extends the parameters a bit by allowing PGD testing for sex-linked genetic disorders and for chromosomal abnormalities. Italy took a much stronger stance on the issue by passing 2004 legislation that

specifically prohibits PGD. This ban was part of a very restrictive law that also requires IVF of no more than three ova at a time as well as the simultaneous transfer of all created embryos into the uterus. These requirements have led to implantation and in some cases abortion of embryos that were later discovered to be affected with thalassaemia. The strictness of the law has caused many Italian couples to go elsewhere to seek reproductive help. The Italian law, as strict as it seems, follows in the footsteps of Germany's law which states that the only treatment allowed to be done on embryos are those treatments that work to ensure embryo survival (Dickens, 2005).

PGD regulation in the United States has considerably fewer rules than in the UK or other parts of the world. In fact, it is one of only a few countries that allows nonmedical sex selection. Vardit Ravitsky, a bioethicist at the University of Pennsylvania commented on U. S. regulation saying, "Today, in this country, the clinics are the gatekeepers. If you have cash and can find a clinic to provide the service, you can get it, whether it is a test for Huntington's disease or sex selection" (Singer, 2007). Some professional societies such as the American Society for Reproductive Medicine offer "professional opinions" on issues surrounding the ethical use of PGD; however, it is evident that voluntary guidelines will not be enough to guide and regulate a profit driven industry. The U.S. needs to establish a foundation of regulations concerning PGD use before technology inevitably opens the ethical "flood gates" and all hope of successful regulation is lost (Singer, 2007).

Personal Conclusions

Before completing in depth research on PGD and the process of creating Savior Siblings I was unsure of where I personally stood concerning the issue. As a science-minded person I strongly believe in taking advantage of technological advances for the betterment of society; however, as an ethical, religious person I could not determine where I felt the line should be drawn. Upon completion of my research I concluded that I support the use of PGD for therapeutic and diagnostic purposes; however, I am against its use for enhancement purposes. Furthermore, I concluded that PGD with tissue typing in order to create Savior Siblings is a morally acceptable use of technology since the purpose is to save the life of a human being. I do, however, believe that regulations are needed to keep the use of PGD from sliding down the slippery slope towards the creation of “designer babies.”

I believe that the use of technology to prevent passage of genetic and chromosomal disorders to future offspring is a responsible use of the advancements in the field of science. I support the argument of many PGD proponents that the failure to use PGD technology for therapeutic purposes would be refusing to use knowledge and capabilities to save lives. As far as PGD for enhancement purposes, I feel this would constitute using science in an unethical manner and should not be allowed. I believe that regulations are needed to outline the acceptable uses of PGD and Savior Sibling technology in order to prevent a morally corrupt charge towards creating a future of perfect children.

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